POTEG is a prognostic biomarker for ESCC

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Esophageal Squamous-cell Carcinoma (ESCC) is a dominant histological subtype of esophageal cancer in China. The high incidence of ESCC in certain ethnic groups and locations is affected by environmental factors (alcohol and tobacco consumption) [1]. Familial aggregation and many studies indicate that genetic susceptibility, such as aberrant activation of oncogenes and inactivation of tumor suppressors, are related with the ESCC tumorigenesis [2]. POTE ankyrin domain family member G (poteg), also known as POTE-14 or ANKRD26-like family C member 2, is located at *14q11.2* [3]. It belongs to POTE family. In human genome, the POTE gene family is composed of at least 13 highly homologous paralogs with preservation of ORFs and splice junctions. The 13 POTE genes are dispersed among eight different chromosomes (2, 8, 13, 14, 15, 18, 21, and 22) and genomic sequence comparison suggests that POTE family genes may evolve from duplicating and remodeling ancestral genes *ANKRD26* and *ANKRD30A* [4,5]. POTE proteins contain three domains: cysteine-rich domains, ankyrin repeat motifs and spectrin-like helices. The NH_2-terminal cysteine-rich domain has an extracellular domain without a signal sequence [3,6]. Each ankyrin repeat motif contains a 33-amino acid sequence motif and the structure mediates protein–protein interactions. This protein recognition module is involved in various cellular functions, and consequently, defects in ankyrin repeats are related to a diverse set of human diseases [7]. The spectrin-like helices are similar to the α-helical coiled coil domain of spectrins which play an important role in building up the membrane skeleton [8]. The presence of ankyrin repeat motifs and spectrin-like helices in a single protein, and the observation that these proteins are associated with plasma membrane, suggest that POTE family proteins might facilitate or intercept signal transmission across the plasma membrane [3,9]. The POTE mRNAs were found in a very limited number of human normal tissues including prostate, testis, ovary and placenta [4]. However, POTE family members are expressed in many kinds of human cancers (colon, lung, breast, ovary, and

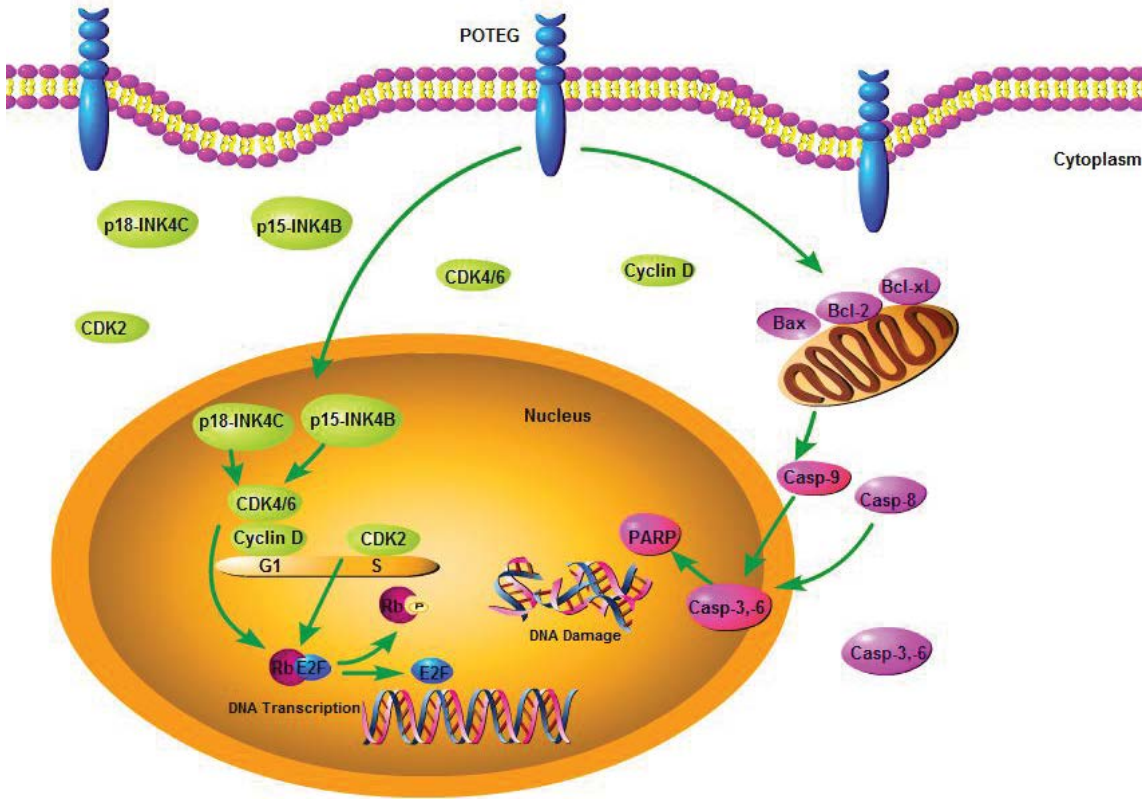

Figure 1) *Summary of the mechanism of POTEG suppressing ESCC cell proliferation.*

POTEG down-regulates CDK2, CDK6, cyclin D1 and further reduces Rb phosphorylation and finally G1/S transition is blocked; POTEG also induces apoptosis by activating caspases and decreasing anti-apoptotic proteins.

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pancreas) [10]. A PCR-based analysis was employed and found that the mRNA levels of POTE-2α, POTE-2β, POTE-2γ, and POTE-22 were predominantly upregulated in cancers compared to normal tissues [10]. A study indicated that deletion of *15q11.1-q11.2*, a region encompassing NBEAP1and POTEB, might be associated with diffuse lymphangiomatosis [11]. Low serum POTEE is a positive prognostic factor for Progression-free Survival (PFS) in Non-small Cell Lung Carcinoma (NSCLC) patients [12]. In glioma patients, POTEH with promoter hypomethylation accounts for POTEH overexpression and poor clinical outcome [13]. And also, our research indicated that POTEG protein level was down-regulated in about 60% ESCC tumor tissues as well as in most ESCC cell lines. The multivariate analysis suggested that POTEG was an independent prognostic marker in ESCC patients [9]. Down-regulation of POTEG is significantly correlated with tumor cell differentiation, lymph node metastasis and advanced clinical staging [9]. Some POTE family members are highly expressed in primary spermatocytes, which are undergoing apoptosis during maturation, suggesting their important roles in inducing programmed cell death [14]. The specific mechanism of its pro-apoptotic function is related to the expression of endogenous POTE-actin fusion protein [15,16]. According to our results, the pro-apoptotic effect of POTEG is also related to activated caspases and decreased anti-apoptotic proteins [9]. Actually, POTEG suppresses ESCC tumor cell growth not only by pro-apoptotic effect but also by blocking G1/S transition. It down-regulates CDK2, CDK6, cyclin D1, and further reduces Rb phosphorylation [9]. As we know, cancer is developed from uncontrolled proliferation of tumor cell with relevant to aberrant activity of specific cell cycle proteins. In the late G1 phase, Rb plays a key role in regulating G1/S transition (a key checkpoint for cell cycle) and following controlled cell progression. Rb, phosphorylated by several cyclins and CDKs, is dissociated from transcription factor E2F, promoting the transcription of S-phase genes which stimulate cell growth [17,18]. POTEG down-regulates Rb phosphorylation and the blocking activity of E2F increases, and consequently ESCC cells growth is inhibited [9,18] (Figure 1). Metastasis is one of the leading causes of cancer-related deaths. A paralog of POTE, POTEF, inhibits metastatic of triple-negative breast cancer cells through regulating *Ricinus communis* agglutinin I (RCA-I) [19]. Our correlation study also revealed that down-regulation of POTEG was significantly correlated with lymph nodes metastasis in ESCC patients [9]. POTEG orverexpression could inhibit ESCC cells' motility in vitro and in vivo by inhibiting EMT (Epithelial-Mesenchymal Transition) [9]. EMT is a critical process in embryonic development and now widely reported to play a prominent role in the tumorigenic process by which cancer cells gained motility and invasiveness [20,21]. Taken together, POTEG is a prognostic biomarker for ESCC and plays a critical role in inhibiting tumor cell proliferation and metastasis. Investigating the tumor suppressor gene poteg might shed light on an effective therapeutic strategy for ESCC patients.

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